Interpreting Human Biomonitoring Data in a Public Health Risk Context Using Biomonitoring Equivalents

ICCA/EPA Symposium:
Public Health Applications of Human Biomonitoring

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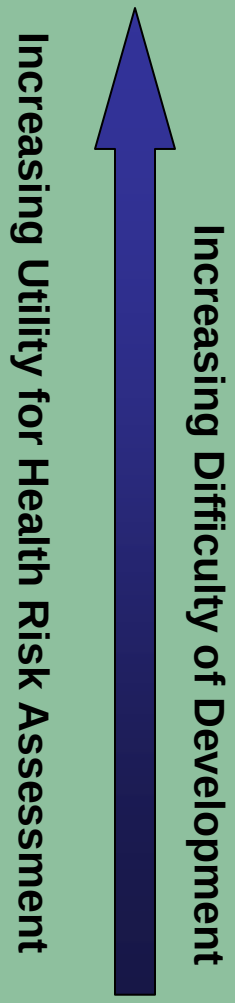
SUMMIT TOXICOLOGY

Reasons for Conducting Large Scale Population Based (Environmental) Biomonitoring Studies -- CDC

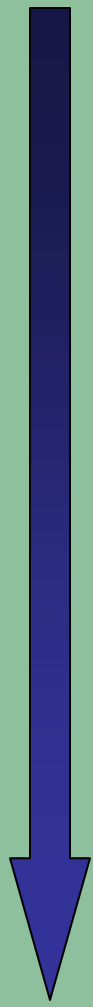
- Determine which chemicals get into members of the general population and at what concentrations
- Determine if exposure levels are higher in some groups than in others
- Track temporal trends in levels of exposure
- Assess the effectiveness of public health efforts to reduce exposure
- Establish reference ranges
- Determine the prevalence of people with levels above known toxicity levels
- Set priorities for research on human health effects

Source: (CDC, 2005)

Risk Assessment Based Methods Used to Interpret Biomonitoring Results



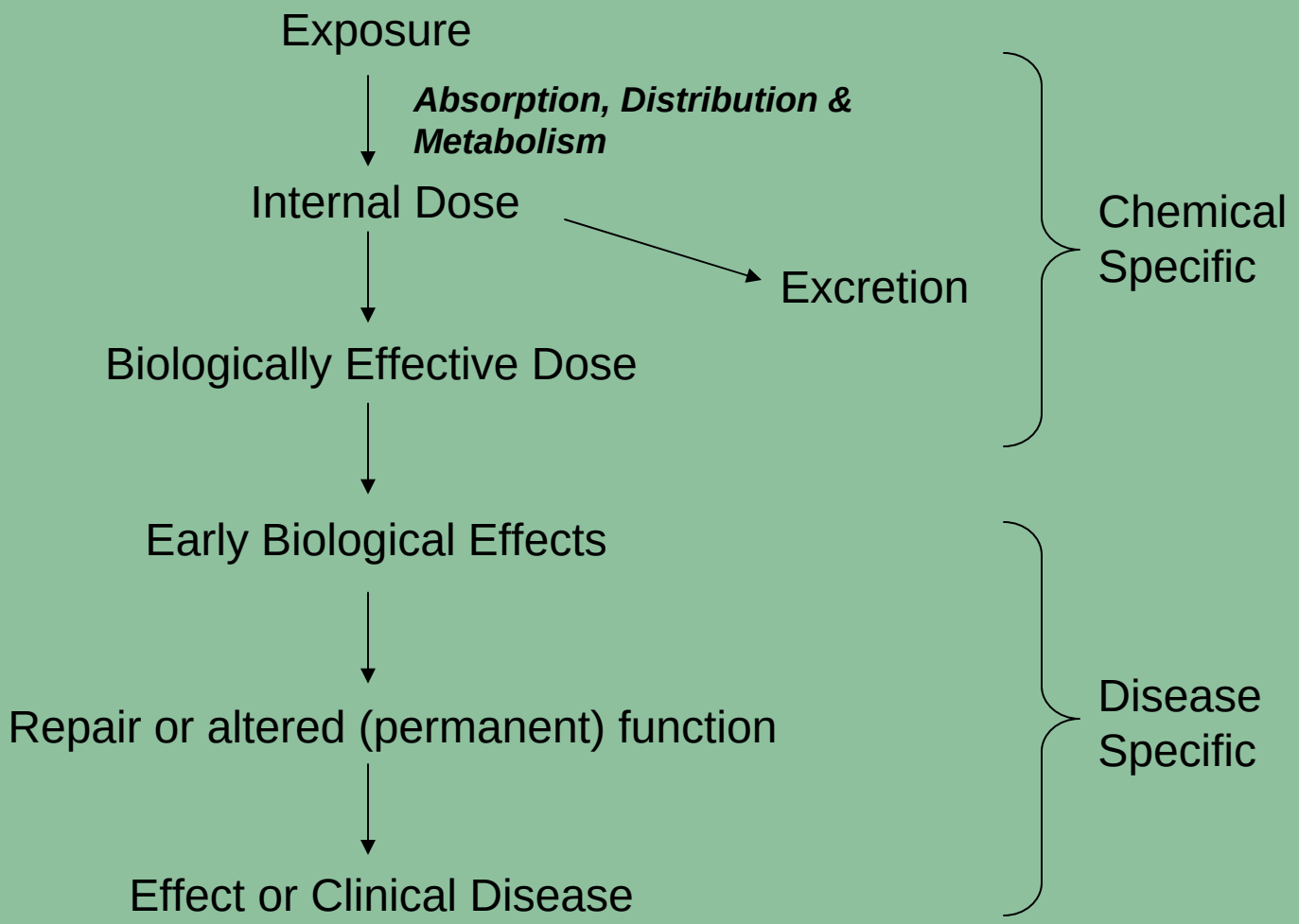
- Predictive
  - Epidemiology-based biomonitoring guidance values (e.g., lead, ethanol, mercury)
    - Usually robust, but take many years to develop
    - Requires robust datasets on biomonitoring-based epidemiology studies
- Screening
  - Internal-dose based risk assessment
    - Can be very sophisticated and robust
  - Forward & Reverse Dosimetry: Leverage existing risk assessment paradigm
    - Can be easy
  - Generic screen:
    - Leverage limited toxicology database
    - Threshold for Toxicological Concern
      - Something is needed for the “data poor” compounds



With Perfect Knowledge

- Epidemiology based standards
  - Great, but takes a long time to build robust database on biomonitoring based epidemiology and to build consensus
- Internal dose based risk assessments
  - Informed by an understanding of
    - Mechanism of action
    - Critical dose metric
    - Species differences in pharmacokinetics
    - Species differences in pharmacodynamics
  - Basis of drug development industry

Relating Exposure & Effect



"The closer the human exposure estimate is to the toxicity endpoint the more accurate the exposure estimate must be" Linda Sheldon

Recent Publication

"Biomonitoring Equivalents: A Screening Approach for Interpreting Biomonitoring Results from a Public Health Risk Perspective" - Hays et al., 2007, *Reg. Tox. Pharm*. Vol. 47, pp. 96-109.

- Presents rationale, background, and methods for development of biomonitoring equivalents (BEs):

- The concentration of a chemical in a (human) biological medium consistent with exposure at an exposure guidance value (e.g., RfC, RfD, UCR, MRL, TDI, etc.)

Forward Approach: Moving from RfD Based on Administered Dose to Screening Blood Levels

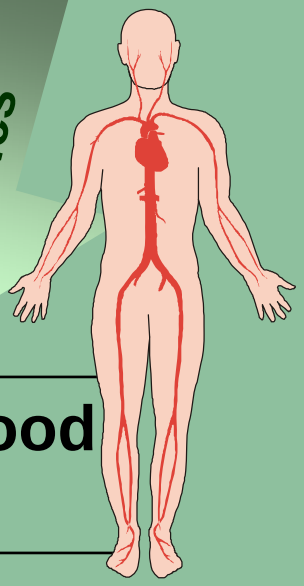
Rat Dose NOAEL/LOAEL

Safety Factors

"Safe" Human Dose – RfD, MRL

Animal Pharmaco-kinetics

Human Pharmaco-kinetics



Rat Blood Level

Modified Safety Factors

Human Blood Level

Questions Raised by BE Paradigm

Rat Dose NOAEL/LOAEL

Safety Factors

“Safe” Human Dose – RfD, MRL

What types of exposure guideline values should be used?

Animal Pharmaco-kinetics

Human Pharmaco-kinetics

How do we use BE_{POD}?

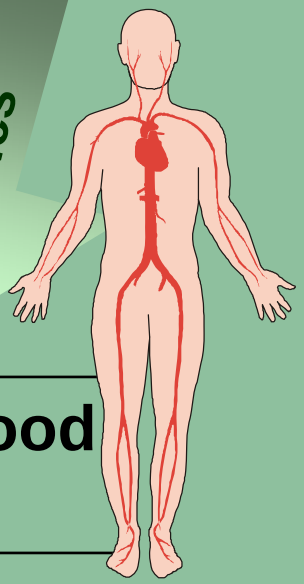
Are there Uncertainty Factors (UFs) built into the external exposure based risk paradigm that should be replaced with modeling internal doses (e.g., PKA-H, PKH)

Does one pathway (animal or human) provide more reliable means of extrapolation over the other?

Rat Blood Level

Modified Safety Factors

Human Blood Level



Additional Questions Raised by Original BE Paradigm

- Does the cancer slope factor approach pose unique challenges?
- How should BEs for short-lived compounds be derived?
- How should these BEs be communicated to the various audiences?
  - What is a BE?
  - What does it mean if biomonitoring levels exceed the BE?

BE Pilot Project

- Sponsoring partners
  - EPA, Health Canada, ACC, CropLife America, RISE, API, Soap and Detergent Association
- Develop guidelines for derivation and communication of BEs
- Expert workshop held June, 2007
  - Participants from government, academia, industry, NGOs
  - Addressed charge questions
  - Informed by draft BEs for four case study compounds: 2,4-D, acrylamide, cadmium, and toluene
  - Develop guidelines for BE derivation and communication

BE Pilot Project - Publications

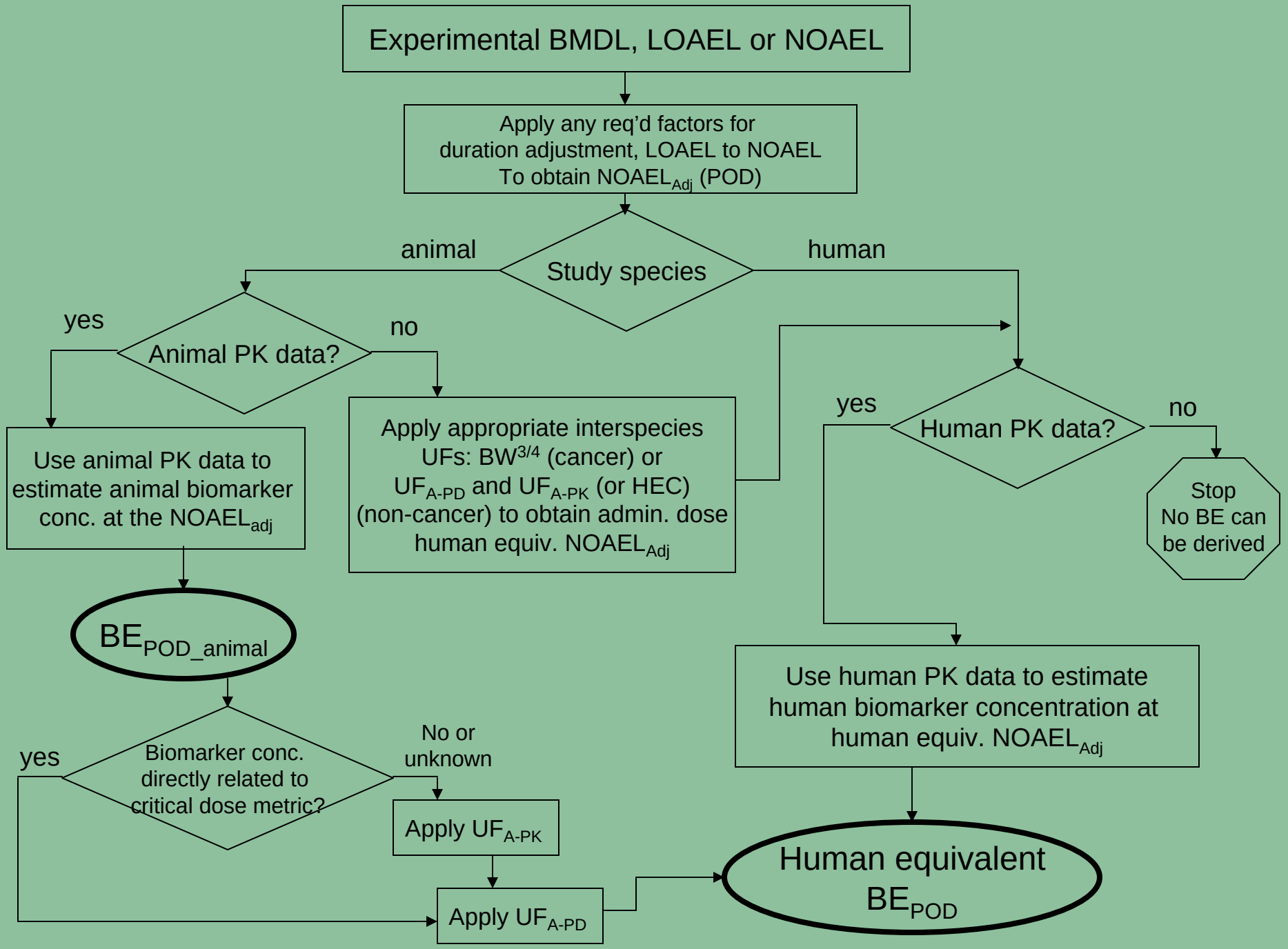
- Dedicated issue of *Regulatory Toxicology and Pharmacology*, early 2008
- Guidelines Manuscripts
  - Technical derivation guidelines
  - Communication guidelines
- Case Studies
  - Toluene
  - Cadmium
  - Acrylamide
  - 2,4-D

Findings From Expert Workshop: Derivation

- Calculate BE values associated with
  - $BE_{POD\text{-}Animal}$ - POD in animals
    - Biomarker concentration expected in animals at POD (NOAEL or BMDL)
    - Duration- and LOAEL-to-NOAEL adjustments already incorporated
  - BE_{POD_Human} - Human equivalent POD
    - Includes adjustment
      - Interspecies pharmacodynamic sensitivity
      - HEC conversion based on PK differences (if appropriate)
  - BE – Fully populated BE
    - Accounts for
      - Intraspecies pharmacodynamic sensitivity
      - Intraspecies variability in pharmacokinetics (if appropriate),
      - Database uncertainties (if appropriate)

Key Considerations for Derivation

- Availability of animal and/or human PK data/model
- Understanding of MOA and critical dose metric
- Understanding of relationship between biomarker and critical dose metric


Experimental BMDL, LOAEL or NOAEL
Apply any req'd factors for duration adjustment, LOAEL to NOAEL To obtain NOAEL$_{Adj}$ (POD)
Study species
animal
human
Animal PK data?
yes
no
Use animal PK data to estimate animal biomarker conc. at the NOAEL$_{adj}$
Apply appropriate interspecies UFs: BW$^{3/4}$ (cancer) or UF$_{A-PD}$ and UF$_{A-PK}$ (or HEC) (non-cancer) to obtain admin. dose human equiv. NOAEL$_{Adj}$
Human PK data?
yes
no
Stop No BE can be derived
BE$_{POD_animal}$
Biomarker conc. directly related to critical dose metric?
yes
No or unknown
Apply UF$_{A-PK}$
Apply UF$_{A-PD}$
Use human PK data to estimate human biomarker concentration at human equiv. NOAEL$_{Adj}$
Human equivalent BE$_{POD}$

Is the BE Approach Practical?

- Requires existing toxicity guidelines and some pharmacokinetic understanding
  - CDC currently has about 460 chemicals on its analyte list
  - An initial survey shows that toxicity criteria such as RfDs and RfCs have been set for at least 150 compounds;
  - Another 40 to 60 represented by criteria for a parent compound (i.e., the analytes are metabolites of compounds with toxicity values)
- Pharmacokinetic data or models are available for many compounds of interest

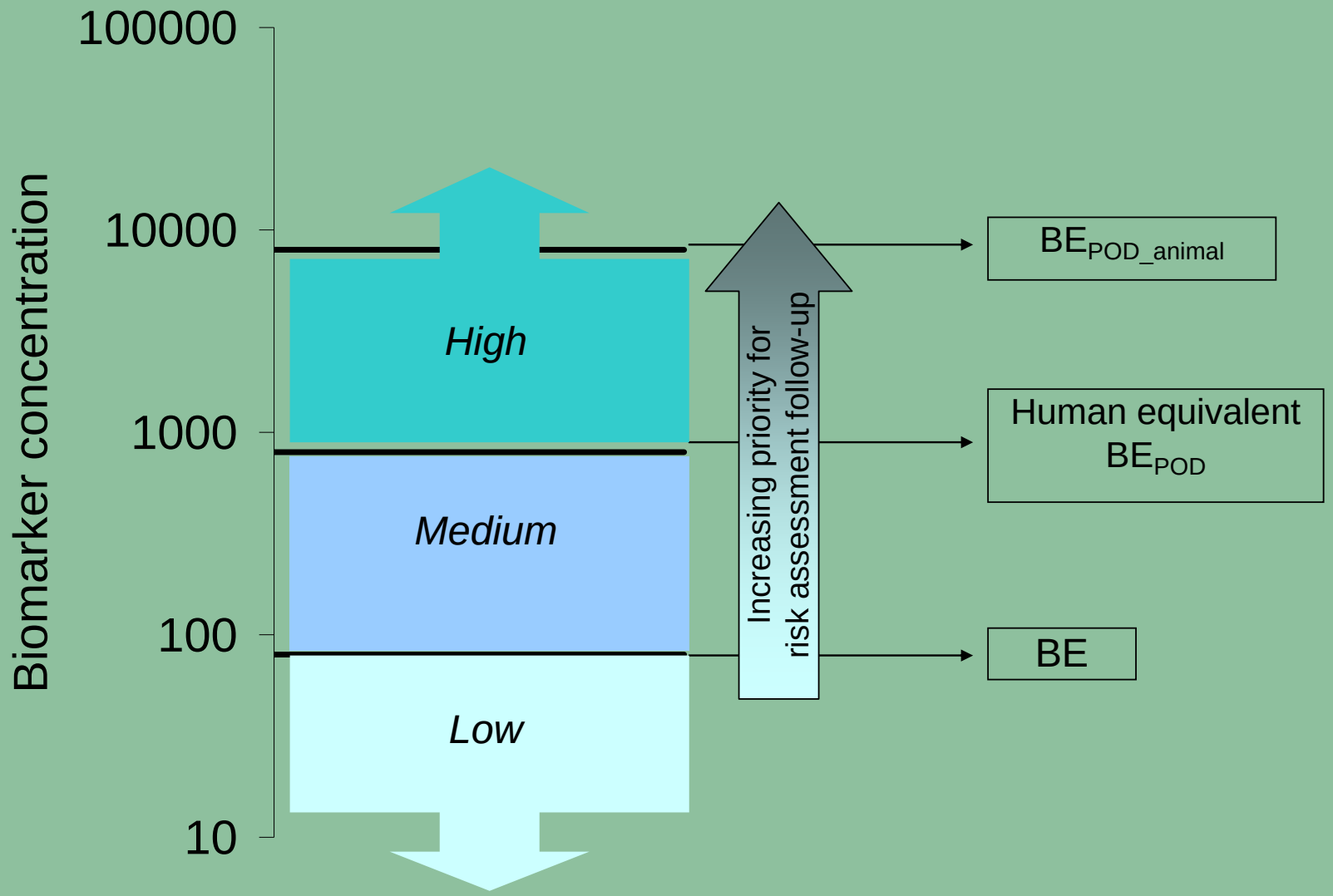
Approaches for Data-Poor Compounds

- BE approach does NOT require robust PBPK models
- Where no PK data exist, bridging studies can be conducted
  - Replicate key animal toxicity study dosing regimens
  - Measure blood concentrations
  - Provides an internal dose metric to facilitate extrapolation to target human blood concentrations
- Where no health-based guidance values exist, develop target MOEs from available toxicity data
  - Provisional approach to allow screening
  - NOT a definitive risk assessment

Findings From Expert Workshop: Communication

- BEs are not bright lines between safe and unsafe levels
- Should not be used for interpreting biomonitoring data from individuals
- Interpretation focuses on low to high priority for “risk assessment follow-up”

BE Communication Model



Case Study

Toluene Biomonitoring Data

- Sexton et al. (2005)
- Elementary school-aged children (n=60 to 160)
- Four samples during two seasons over two years

Blood toluene	
Median (ug/L)	Upper 95th (ug/L)
0.10	0.25
0.08	0.20
0.11	0.19
0.17	0.37

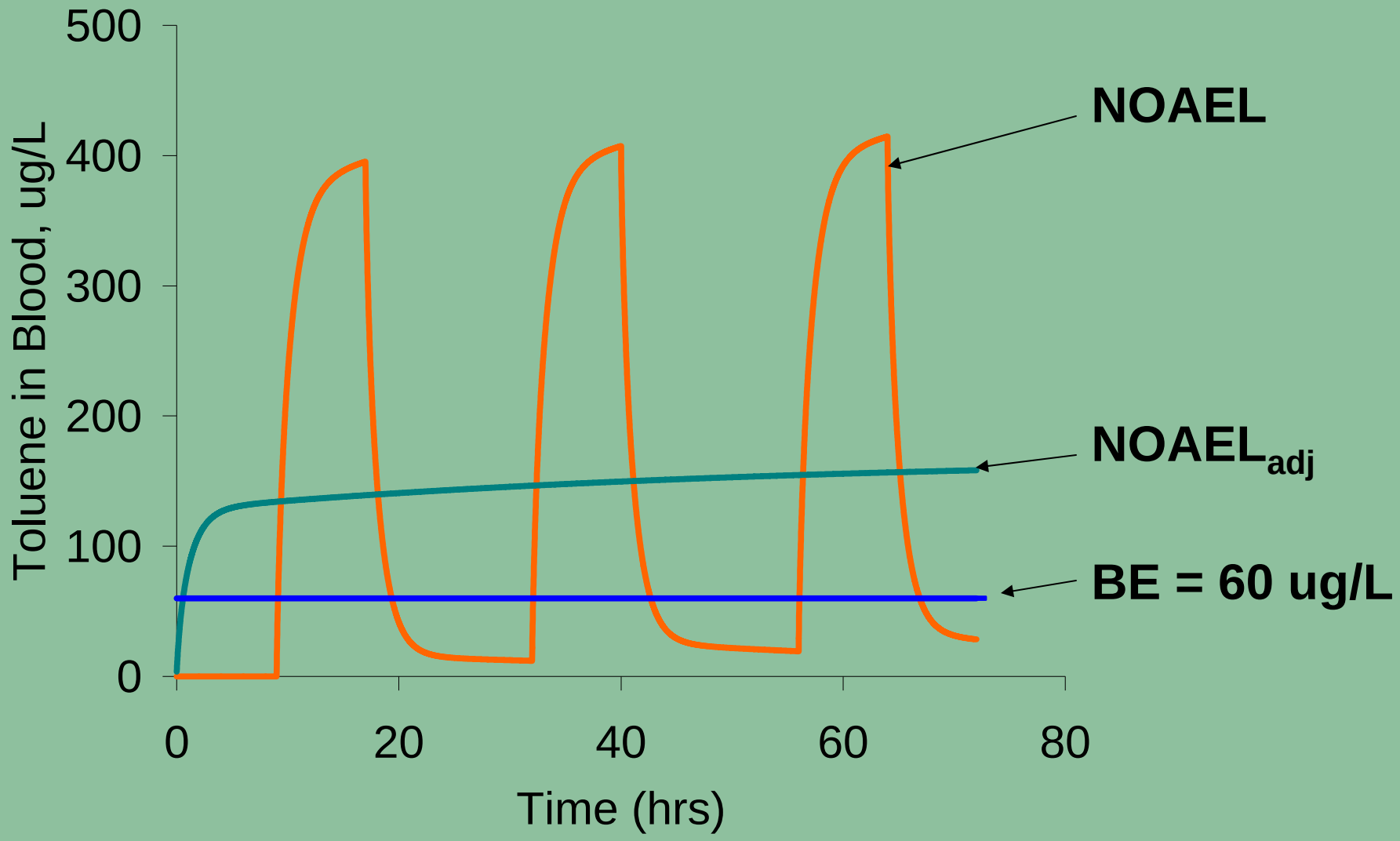
Example: Derivation of a BE_{RfC} for Toluene

- USEPA RfC
  - Based on NOAEL for neurological effects in multiple human occupational studies
  - Toluene blood concentration relevant to effects
- Pharmacokinetics of toluene well understood
  - Human and animal PBPK models available

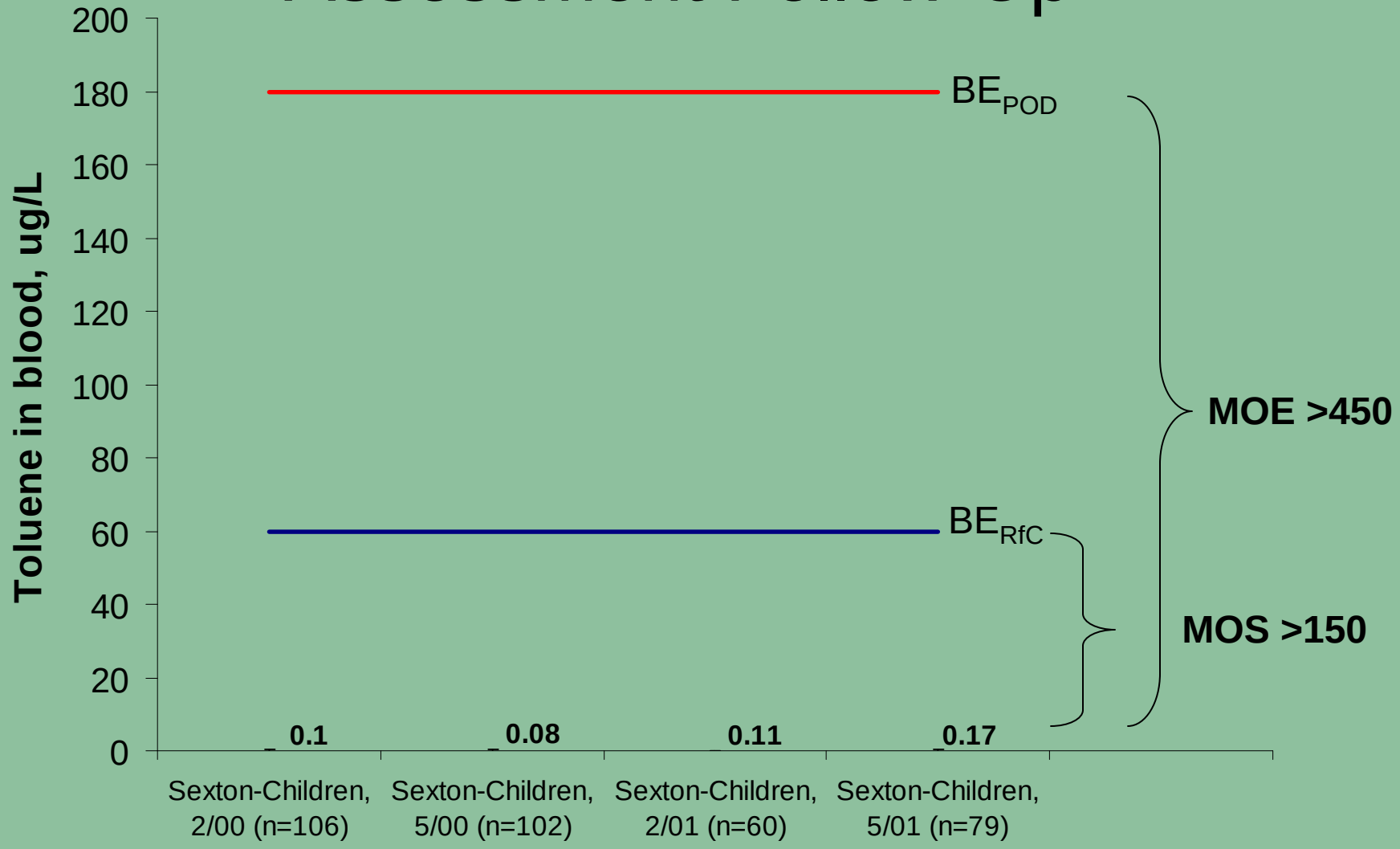
Derivation of RfC and BE_{RfC}

	RfC
Human NOAEL	128 mg/m^3 8 hrs/d, 5 d/wk
$NOAEL_{adj}$	46 mg/m^3 continuous exposure
Uncertainty factors:	10 3 for P-D 3 for P-K
Result	**5 mg/m^3**

Estimated Blood Concentrations of Toluene



Interpreting Biomonitoring Data and Communicating Priority for Risk Assessment Follow-Up



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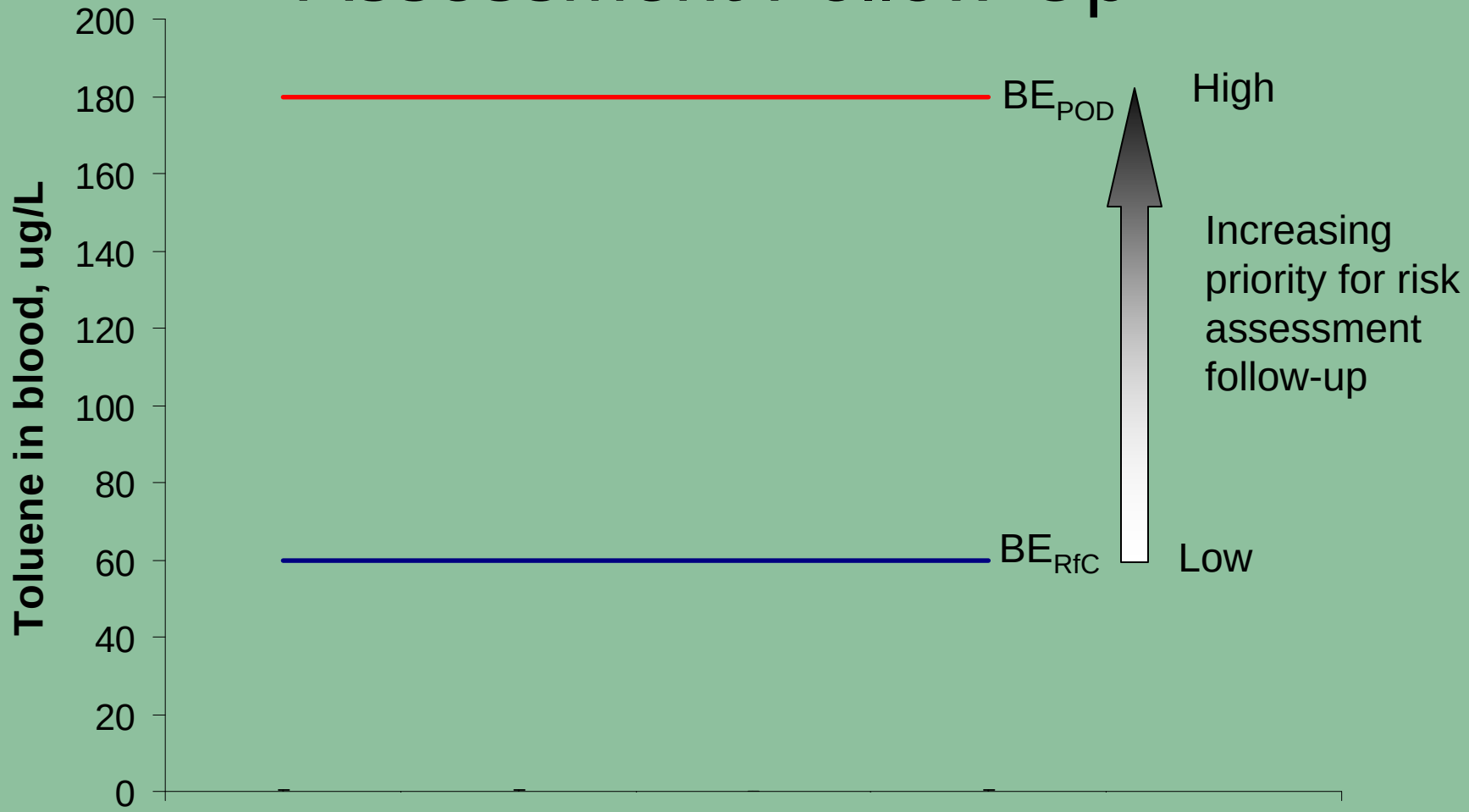

The Value of the BE as a Screening Tool

- **Risk Assessment**
  - Identify areas of potential improvement for risk assessments
- **Biomonitoring Studies**
  - Identify preferred biomarker(s)
  - Identify concentrations of interest (LOD)
- **Risk Communication and Context**
  - Provide context for biomonitoring study results
- **Risk Management**
  - Prioritize risk assessment and research efforts
    - Compounds with low margin of safety – potentially invest in risk assessment follow-up (exposure and epi studies)
    - Compounds with large margin of safety – move to lower priority list
    - Identify types of studies/data that will reduce uncertainties